Nanomedicines for the treatment of infectious diseases: Formulation, delivery and commercialization aspects

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Abstract

The increasing prevalence of drug resistant pathogenic strains, including multi drug resistant TB along with the growing HIV and malaria resistance demand new routes of innovation for pharmaceutical drug discovery. Nanomedicine provides the opportunity to develop therapies for infectious diseases with reduced drug dosage and dose frequencies and shortened treatment duration. These combined strategies may lead to an increase in patient compliance with the goal of improving treatment outcomes and reducing occurrences of drug resistance. With these exciting opportunities, due attention has been given to the clinical translation of nanomedicines for infectious diseases applications. Examples are presented that demonstrate how nanomedicine strategies can enable the development of a wide range of therapeutic solutions to curb the rise of the infectious disease epidemic. The chapter also discusses the models for development and commercialization of medicines for infectious diseases, and presents considerations for commercialization of nanomedicines for infectious diseases.

1. Introduction

An infectious disease is defined as a disease that can be transmitted from person to person or an animal to a person or vice versa. Common modes of transmission include coughing, sneezing and exchange of body fluids. In a broad sense what differentiates this definition of an infectious disease from a hereditary disease is that in the case of infectious diseases, a pathogen or causative organism is involved and that pathogen is transmitted or spread through humans, animals or vectors such as insects while a hereditary disease is inherited from one's parents (Nash, Dalziel, and Fitzgerald 2015). Table 1 lists some of the most common infectious diseases, the pathogen involved, and the major transmitting agent.

Insert Table 1 here

Over 200 infectious diseases are known to man. However, there are a handful of infectious diseases which are responsible for significant morbidity and mortality globally, and these include HIV/AIDS, TB and malaria. Outbreaks of infectious diseases are also not uncommon. For example, in 2014, West Africa experienced the largest Ebola outbreak in history. This outbreak claimed close to 30 000 lives before containment (Spengler et al. 2016). The disease was able to spread to parts of Europe and the United States. There have also been other deadly outbreaks in recent history, including the Zika virus outbreak emerging from South America, and the Avian flu outbreak emerging from Asia (Brasil et al. 2016, Xie et al.).

HIV/AIDS, TB and malaria combined, accounted for over 2.7 million deaths worldwide in 2018 (WHO 2020, 2019a, b). HIV-1 is ranked globally as the deadliest single most infectious agent, with *Mycobacterium tuberculosis* (*M.tb*) following a close second (WHO 2020). HIV/AIDS is no longer a death sentence, but there is uncertainty concerning the access and sustainability of long-term treatment, especially in resource-limited settings. HIV-1 is one of the major co-infections in patients with TB, and this population is several times more likely to develop active TB disease than people without HIV-1 (WHO 2019a). An estimated 1.7 billion people worldwide are infected with *M.tb* and do not show symptoms of active disease (latent infection) (WHO 2019a). Latently infected persons are at risk of developing active TB during their lifetime and thus spreading the disease, especially when immunocompromised, as in the case of concurrent HIV-1 infection. Malaria is also among the world's deadliest infectious disease. Annually, over 1.5 million people die and an estimated 40% of the world's population is at risk. Over 90% of deaths occur in sub-Saharan Africa (Alonso et al. 2011, Fong 2013). Children under five years and pregnant women are most at risk. On average a child dies of malaria every 12 seconds and children surviving are at an increased risk of long term neurological and cognitive disabilities (Idro et al. 2010, Snow et al. 2005). Over 100 000 new-born deaths each year are attributed to malaria in pregnancy (Desai et al. 2007). Consequently, malaria has a huge societal and economic impact globally, and in Sub-Saharan Africa in particular.

2. The need for nanomedicines for infectious diseases

Several drugs are available for the treatment of infectious diseases. The drugs are used alone, or more commonly, in combination, in what are known as 'drug cocktails'.

Administration of drugs as cocktails assists in killing various life stages of the pathogen concurrently. For example, in the case of TB treatment, some drugs target persistent bacterium, while others may target the rapidly replicating bacterium (Janin 2007). Cocktails also assist to reduce the generation of drug resistant pathogen strains. Existing drugs are generally potent at killing the pathogen. Therefore, it is not so much a case of needing new drug compounds, but it is also a case of effective use of existing drugs. Examples of general limitations faced by the drugs include poor oral bioavailability, short plasma half-life, high plasma protein binding and poor penetration across the blood brain barrier (Kutscher et al. 2016, Dube et al. 2013). For most infectious diseases, the pathogen predominantly resides within the intracellular space, and this poses an additional barrier for the drug compound to penetrate (Armstead and Li 2011). Other limitations include severe adverse effects, poor availability of patient friendly dosage forms, e.g. dosage forms for paediatrics, which affects patient compliance towards treatment regimens (Sosnik and Carcaboso 2014). Overcoming these challenges could improve treatment compliance, the manner in which the drug is taken, and the efficacy of the drug (Sosnik et al. 2010) and improve treatment outcomes and reduce morbidity and mortality from these diseases. Improved drug delivery would be expected to work in conjugation with other public health measures to reduce transmission and deaths and move towards disease eradication, e.g. efforts to increase insecticide spraying in high mosquito burden areas, and improving awareness of the need for hand-washing. There have been extensive efforts to improve dosage forms for infectious diseases, and one notable example is the development of fixed dose combination tablets for TB and HIV therapy, with resultant improved patient compliance (Bangalore et al. 2007). However,

infectious diseases continue to pose a global threat and their spread can be attributed to ineffectiveness of current treatment regimens, increased international travel and trade, migration and increasing antimicrobial resistance.

Vaccine development is a major focus in the development of therapies for infectious diseases (Røttingen et al. 2017). There is currently no approved vaccine for HIV or malaria, and the vaccine for TB, i.e. the *bacillus Calmette-Guérin* (BCG) vaccine is generally ineffective. Recent Phase III clinical trials on the most promising candidate malaria vaccine RTS,S/AS01E indicate limited long-term efficacy, with the vaccine providing 43.6% protection in the first year and zero protection by the fourth year (Olotu et al. 2013).

Nanomedicine has the potential to address the challenges faced by therapeutics for infectious diseases, for example reformulating drugs to provide effective therapies in patient convenient dosage forms and regimens, across the range of therapeutic interventions (Andrade et al. 2013, Sosnik et al. 2010, Dube 2019). Nanomedicine is a relatively new technology utilizing nanometre scale particles to improve drug delivery, i.e. pharmacokinetic profiles, achieve organ, cell or pathogen targeting and reduction in drug toxicity and to improve diagnostic capability (Moghimi, Hunter, and Murray 2005). Nanomedicine has already impacted other diseases, e.g. cancer, exemplified by the reformulation of doxorubicin to provide a potent, extended half-life therapy with reduced side effects (Bobo et al. 2016, Anselmo and Mitragotri 2019). A review of US Food and Drug Administration (FDA) approved nanomedicines by Bobo et al (2016) reported that out of 52 approved nanomedicines on the market, only 4 are intended for the treatment

of an infectious disease (Bobo et al. 2016). The disease conditions targeted for treatment by these nanomedicines are fungal infections (i.e. AmBisome® and Abelcet®) and Hepatitis B and C (i.e. Pegasys® and PegIntron® for Hepatitis C treatment) (Bobo et al. 2016). In 2019, Anselmo and Mitragotri reported at least two nanomedicines that are currently in clinical trials for an infectious disease (Hepatitis B and pneumonia) (Anselmo and Mitragotri 2019). Juxtaposed against the global morbidity and mortality of infectious diseases, and the challenges faced by existing drugs, there is therefore the need to develop more nanomedicines for the treatment of infectious diseases. Nanomedicine has likelihood to do the same for infectious diseases, as it did for cancer, radically improving treatment outcomes using currently available drugs, saving lives, and moving towards complete eradication of these diseases. There is significant ongoing infectious disease drug development (Nordling 2013) and nanomedicine research occurring on the African continent (Dube and Ebrahim 2017, Saidi, Fortuin, and Douglas 2018). Researchers in Africa are key in infectious disease research, as the continent bears the greatest burden of infectious diseases and researchers also have access to patient populations for clinical studies. However, it is hoped that more countries in the world will extensively engage in the development of nanomedicines for infectious diseases, as this issue is a global concern. Some issues around ‘attractiveness’ of development and commercialization of medicines for infectious diseases are discussed in section 4 of this review.

3. Nanoparticles as drug delivery systems and applications in infectious disease treatment

A variety of organic and inorganic biomaterials have been developed as delivery systems, from the first liposomal system described in 1965 to more recent systems with capabilities

of stimulating therapeutic release and action in response to interactions with the surrounding environment. This section will review some of the common nanoparticle types and their formulation and describe some studies in which the nanoparticles were investigated for infectious disease therapy. Due to the broadness of the infectious disease field, the examples provided herein are derived from studies directed towards HIV, TB and malaria treatment. Due to the intracellular residence of infectious disease pathogens, the design of nanoparticles should facilitate entry into the intracellular space and potentially including the nucleus (Figure 1).

Insert Chapter 12 Figure 1 here

3.1 Liposomes

Liposomes are spherical vesicles consisting of phospholipid bilayers capability to entrap water soluble drugs in the hydrophilic compartment and hydrophobic drugs in the lipid layers. They therefore present opportunity to deliver drug cocktails of both hydrophilic and hydrophobic drugs. Drug delivery with liposomes has been widely investigated and has had numerous commercial applications including in infectious diseases (Zazo, Colino, and Lanao 2016). One such example is AmBisome® (liposomal Amphotericin B), approved by the FDA in 1997 for the treatment of fungal and protozoal infections. Liposomes have been also used to deliver latency activators to CD4+ T cells for the treatment of HIV (Kovochich, Marsden, and Zack 2011). Kovochich *et al.* reported liposome-based co-delivery of nelfinavir and bryostatin-2 and consequent activation of latent virus and inhibition of virus spread (Kovochich, Marsden, and Zack 2011). Mannose decorated liposomes have been used by Chono *et al.* to achieve increased ciprofloxacin levels in macrophages and in plasma (Chono et al. 2008). Greco *et al.* constructed Janus

faced liposomes for TB treatment. The liposomes were constructed with external phosphatidylserine (induces phagocytic recognition and engulfment) and internal phosphatidic acid (promotes phagolysosome maturation). These liposomes could be taken up efficiently by macrophages leading to increased intracellular killing of *M.tb* (Greco et al. 2012).

3.2 Polymeric nanoparticles

Biodegradable polymeric particles offer enhanced stability of drugs, biocompatibility with tissues and cells and controlled release of bioactives (Kumari, Yadav, and Yadav 2010). Various methods of synthesis have been developed leading to polymeric nanoparticles tailor-made according to the need of application and the drug to be encapsulated. Polyesters have been the most studied and well characterised of the synthetic biodegradable polymers and among them poly (ε-caprolactone) (PCL), poly (lactic acid) (PLA), poly (glycolic acid) (PGA) and their copolymer poly (lactic acid-co-glycolic acid) (PLGA) have received great attention due to better encapsulation, better controlled release and less toxicity (Kumari, Yadav, and Yadav 2010). PLGA has been the most successfully used and has received FDA approval in various drug delivery systems (Danhier et al. 2012). Natural polymers such as alginate, albumin and chitosan have also been used as drug delivery vehicles. Polymeric nanoparticles are typically coated with poly ethylene glycol (PEG) to alter their distribution by enhancing their circulation time and increase the delivery of therapeutic molecules. PEG has the capability to minimise recognition of nanoparticles by plasma proteins and avoid uptake by macrophages for clearance (Semete, Booysen, Kalombo, et al. 2010). Polymeric nanoparticles have been

investigated for anti-TB and anti-HIV chemotherapy; designed to improve the pharmacokinetic profiles allowing for better dosage schedules to reduce cytotoxicity and side effects (Semete, Booysen, Lemmer, et al. 2010, Dube et al. 2014, Makita-Chingombe et al. 2016). Early studies established that encapsulation of anti-tubercular drugs in polymeric nanoparticles could extend plasma concentrations of the drug, and also increase, and extend drug residence time in tissue (Sharma et al. 2004, Gelperina et al. 2005, Pandey et al. 2003). Pandey *et al.* showed that when anti-TB drugs are encapsulated in PLGA nanoparticles and orally administered to mice, the drugs can be detected in plasma and tissues (lung, liver, spleen) for extended periods of time (up to 9-11 days) at concentrations above the required minimum inhibitory concentration. This is in contrast to free drug which was eliminated within 24 h in plasma and 48 h in tissue (Pandey et al. 2003). In a study utilizing *M.tb* infected guinea pigs, Ahmad *et al.* administered nebulized alginate nanoparticles at three doses that were spaced 15 days apart for 45 days, whereas free drugs was orally administered daily for 45 days. The study reported undetectable mycobacterial colony forming units in the lungs and the spleen, suggesting the potential of nanoparticles to modify dosing regimens (Zahoor, Sharma, and Khuller 2005).

In recent times, there has been a shift from utilizing polymeric nanoparticles to modulate intracellular drug pharmacokinetics (Tukulula et al. 2018) and to utilizing the nanoparticles to also activate the innate immune system, i.e. immunotherapy for infectious diseases (Dube and Reynolds 2016, Liu, Pradhan, and Roy 2016, Bekale et al. 2018). Dube *et al.* synthesized a β-glucan functionalized chitosan-PLGA nanoparticles and demonstrated that these nanoparticles activated macrophages, i.e. resulted in a significant

enhancement of reactive oxygen species and pro-inflammatory cytokines including TNF-α production, compared to nanoparticles without β-glucan functionalization (Dube et al. 2014). This study, and that described by Greco *et al*, working with liposomes (Greco et al. 2012), demonstrates the potential of this immunotherapy approach towards eradication of intracellular pathogens.

3.3 Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) are colloidal drug delivery systems consisting of a hydrophobic solid lipid core covered with a monolayer of phospholipid coating (zur Mühlen, Schwarz, and Mehnert 1998). A majority of SLNs are prepared by high pressure homogenization either at temperatures above the melting point of the lipid (hot homogenization) or at cold temperature (cold homogenization) in the presence of a surfactant/stabiliser. Hydrophobic drugs are dissolved in the melted lipid during hot homogenization. Hydrophilic drugs are encapsulated using the cold homogenization technique to partitioning between the melted lipid and the water phase during hot homogenization (Müller, Mäder, and Gohla 2000). Within the antimicrobial field, the therapeutic potential of anti-TB drug loaded SLNs has been investigated (Pandey and Khuller 2005). A SLN formulation was demonstrated to improve half-life of the antimalarial tafenoquine, and also mitigate drug toxicity against red blood cells (Melariri et al. 2015). SLNs have also been used in the intranasal delivery of the anti-HIV drugs, Efavirenz and Tenofovir disoproxil fumarate to the brain; SLNs increased the concentration of drugs available to the brain compared to free drug, however the brain to plasma drug concentration was low due to the presence of the blood brain barrier (Bobo et al. 2016).

3.4 Metallic nanoparticles

Metallic nanoparticles are generally synthesised by the chemical reduction of a chemical salt (gold (Au), silver (Ag), titanium, platinum) with a reducing agent and their characteristics being modified by control of different synthesis conditions such as temperature, pH, reduction time or reducing agent concentration (Mody et al. 2010). Ag nanoparticles have inherent antimicrobial properties and have found their main therapeutic application in the antimicrobial field (Wei et al. 2015). Au nanoparticles have been used to target antibacterial drugs which were linked to the particles through Au-S or Au-amino bonds (Zhao and Jiang 2013, Grace and Pandian 2007). Metallic nanoparticles are also potential anti-tubercular agents. Spherical Au and Ag nanoparticles were reported to display good antibacterial activity against BCG (Zhou et al. 2012). With regards to HIV, Ag nanoparticles have been shown to exert anti-viral action against HIV (Lara et al. 2010). In more recent times, metal organic framework nanoparticles have been explored for targeted delivery of anti-tubercular drugs (Guo et al. 2019, Wyszogrodzka et al. 2018). Due to their safety and high drug loading capacity, these particles are promising next generation drug delivery systems for infectious diseases (Wyszogrodzka et al. 2018).

3.5 Calcium carbonate particles

In recent times calcium carbonate ($CaCO_3$) has gained increasing attention in drug delivery due to its enhanced biocompatibility and biodegradability in comparison to its counterparts (silica nanoparticles, calcium phosphates, carbon nanotubes, hydroxylapatites). $CaCO_3$ can be obtained by precipitation of aqueous calcium and carbonate solutions (liquid-liquid reactions) or carbonation of a calcium solution (gas-

liquid reactions) (Zeynep et al. 2015). Increased interest in bioinspired materials and environmentally friendly processes has recently led to the formulation of $CaCO_3$ particles using supercritical CO_2 ($ScCO_2$) technology. Sc-CO2 is a highly efficient and versatile approach for the synthesis of $CaCO_3$ and offers optimal experimental conditions ideal for sensitive therapeutic compounds (Hassani et al. 2013). $CaCO_3$ particles have been studied for the pulmonary delivery of antibiotics to treat lung infections. Moreover their size (1-5 μm) and their density provide them an excellent mass median aerodynamic diameter, compatible with their local administration as dry powders, a good penetration and retention in the lungs in the presence of airway narrowing (Tewes et al. 2016).

4. Medicines development models and considerations for commercialization of nanomedicines for infectious diseases

A critical component of the research and innovation value chain is the translation of research outputs, and in the case of nanomedicines for infectious diseases, there is critical need for more of this technology to reach the patient. In this section we discuss the various medicine development models that are available and the commercialization considerations that apply to development of medicines for infectious diseases.

The low number of new drug molecules approved for infectious diseases such as TB, malaria, trypanosomiasis, etc., is evidence that drug development for these therapeutic areas remains low priority and is generally considered non-lucrative by the multinational pharmaceutical companies (Pedrique et al. 2013). It is clear from R&D investment

portfolios, that the majority of global spend on R&D goes towards therapeutic areas where there is a strong economic base. Thus, the classical commercialization route, management of intellectual property (IP) and R&D investment levels remain suboptimal for molecules targeting infectious diseases. Conventional medicines development models include, but are not limited to:

- In-house R&D and commercialization of the molecules identified by the pharmaceutical company; investing from lead discovery through to completion of clinical trials
- Acquisition of small biotechnology firms that emerge from university R&D where the molecules were discovered, followed by investment into the clinical trials by pharmaceutical companies
- Management of IP such that it provides exclusivity for a specific period, resulting in monopolies and a pricing model that builds in the cost of R&D into the final product

4.1 Impact of IP on commercialization models for medicines

An important issue relating to biotech companies and the commercialization model to be followed is IP management and exploitation. Depending on the sector, various forms of IP are common, e.g. trade secrets, know-how, lead times, first mover advantage etc. However, in the biotech and pharmaceutical sector, patents are an important financial asset. A patent provides a temporary monopoly to the owner in excluding others from using it and is seen as the largest asset of any biotech or pharmaceutical firm. This short-

term monopoly enables the firm to sustain the economic value of technological knowledge and innovation to enable companies to refund their investment into other innovations, producing a high risk-return ratio. Patents are however granted for a limited period of time, mostly, 20 years. During this time the patent holder may transact using the patent through licensing options (Külpmann 2005). Different countries have patent laws which are a set of legal rules that govern the validity and infringement of patents across a wide variety of technologies (Külpmann 2005). The increase in the number of participants in the IP landscape (producers and users) has resulted in patents becoming a very competitive business tool. Large corporations have progressively developed patent portfolios to strengthen their bargaining and retaliation power or to exercise patent strategies to delude competitors. This competitive climate, has led to an emergence of patent-based business models which exploit the patent values. These business models tend to create more value since they are more effective and efficient at application and exploitation of patents. On the hand, detrimental effects can be noted; particularly the litigation-based business models of patent trolls (Su, Chen, and Lee 2012) and the impact on access models for the products by consumers. These challenges have also been noted in the development of innovative medicines for infectious diseases, where the patenting strategy is not a viable approach for many philanthropic funders due to the impact they have on commercialization models and the cost of the eventual product. Thus the conventional models may have negative effects of slowing down and hampering innovation and patent creation in the infectious disease medicine development space.

4.2 Cost of research and development

It is well understood that R&D is expensive, primarily in the pharmaceutical sector compared to other technology companies. A recent study by DiMasi et al., provides the latest costs of drug development which amount to pre-tax out-of-pocket per approval at USD 1.4 billion (2013 dollars) and pre-tax capitalized per approval is $2.5 billion (2013 dollars) (DiMasi, Grabowski, and Hansen 2016). The study also indicates that costs for compounds that were abandoned were linked to costs of approved compounds, thus resulting in the costs having to be recovered through drug pricing strategies (DiMasi, Grabowski, and Hansen 2016). The reason that society has accepted this model is that there is a clear need for R&D into new medicines. However, such models have led to disparities in access, underutilization of medically important medicines and financial hardships for consumers, including payers and providers.

Furthermore, because of the characteristics (small, costly, negative cash flows, long time to develop a product etc.) of biotech/small pharmaceutical companies, their financing is challenging. Most biotechnology companies also explore the avenue of seeking financing through partnering with larger firms such as multinational pharmaceutical companies. This has recently been the major business and funding strategy for biotech firms, where large pharmaceutical companies have cut their R&D budgets, and are seeking for close to commercial innovations to include into their pipeline (Schiff and Murray 2004).

Therefore, the practice of rewarding pharmaceutical companies, with time-limited marketing monopolies through IP rights management and exploitation can create other problems such as biases in R&D investment that favour therapeutic areas where there are clear economic returns, lead to inadequate investment in early stage R&D.

These two critical aspects, i.e. IP rights and cost of R&D have a major impact on access to medicines and vaccines, and thus there is a need for new innovative approaches to ensure that those that need the medicines and vaccines can access these timeously and cost effectively.

5. New commercialization models

Any new model for the development and commercialization of therapeutics and diagnostics for infectious diseases would require that the model firstly implements innovative mechanisms to manage, transfer and exploit IP. Secondly, innovative financing models for R&D costs, which are typically built into the cost of medicines are required. The critical third aspect would involve innovative mechanisms for access to medicines by patients in the regions most affected. The models described below address these principles to some extent.

5.1 World Health Organization (WHO) expert working group on financing and Coordination (CEWG)

The WHO CEWG demonstration projects were set up as a prototype model that will provide evidence on innovative mechanisms to fund and coordinate public health R&D to address unmet medical needs especially of developing countries using unconventional mechanisms. Furthermore, the CEWG were established to contribute to further discussion on a sustainable global framework for improving access to health care (https://www.dndi.org/2013/advocacy/who-cewg-process-identification-of-health-rd-demonstration-projects/). The main guiding principles of

this model whose implementation, impact and return for the researchers and developers of the solutions is still to be evaluated include:

a. **Open knowledge and innovation:** This principle refers to the open use, generation and management of any IP emanating from joint projects. All partners should ensure that any IP, data, publications etc. are openly shared. Collaborative approaches to addressing the specific challenge are encouraged within this model.
b. **Sustainable financing of the initiatives:** This principle states that members of the initiative, primarily member countries should commit to securing the requisite funding. The source of funding is not restrictive, thus creating room for private public partnerships, and pooling of funds.
c. **Equitable access and de-linkage:** This principle makes a clear requirement for equitable access to the therapeutics or diagnostic tools developed. Integral to this principle is the commitment for production and supply at cost with a minimal margin, registration and availability in all endemic countries, and open licensing of all IP with a possibility of technology transfer. It is anticipated that the policy would facilitate de-linking R&D costs from the final price of the product (discussed further in the third model).
d. **Continuous new incentives**: This principle is in place to foster effective and efficient coordination mechanisms amongst existing organizations and multinational firms to ensure shared value across stakeholders.

5.2 Product development Partnership (PDP): Example of Medicine for Malaria Venture (MMV)

MMV is a leading PDP in the field of antimalarial drug research and development, and aims to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs using innovative partnership and finding models (https://www.mmv.org/about-us). MMV coordinates and works with partners across the drug discovery value chain, spanning from research institutions, multinational pharmaceutical companies across various regions. This model has also been applied by the Global TB Alliance (https://www.tballiance.org/).

MMV and its partners manage a portfolio of 65 projects the largest portfolio of antimalarial R&D, which includes nine new drugs in clinical development. Further details on these new molecules can be accessed on the MMV website (https://www.mmv.org/research-development/mmv-supported-projects) where up to date information is provided. Key to the MMV's success are the following factors:

Firstly, coordination of large multi-country studies and a broad range of partners, which at the time of compilation of this work was about 400 pharmaceutical, academic and endemic country partners in more than 55 countries. Due the socio-economic challenges in the malaria endemic regions, MMV extends its support to work with distribution, pharmaceutical companies and country stakeholders to ensure efficient uptake that will ensure that the most appropriate medicines are available as quickly as possible.

The second key aspect to its success is its funding model. MMV receives sustained funding and support from government agencies, private foundation, international organizations, private individuals and corporate foundations. 60% of the MMV funding comes from the Bill and Melinda Gates foundation and 14.5% from the United Kingdom Department of International Development and the rest from various other funders. These diverse funding streams are used to fund R&D as well as specific targeted access and delivery interventions that aim to make it easier for vulnerable population in endemic countries to access anti-malarial products.

Through this model and since the inception of MMV in 1999, USD 709 million has been invested into building this large portfolio, with six new antimalarial drug being brought into the market and distributed to those that need the drugs the most. MMV estimates, that a minimum of USD 430 million over 5 years would be required to sustain its work and outputs.

5.3 Delinking R&D costs from price of medicines

As discussed in the first model, the management of IP makes the international trade agreements restrictive in that, the exclusive rights regime tends to be very expensive. Thus, the WHO established a Consultative Expert Working Group on research and Development: financing and Coordination (CEWG), whose objective was to explore innovative approaches to manage innovation and access of new medicine innovations. One of the approaches considered is de-linking the cost of R&D from the

price of the medicines. De-linkage is a concept that is strongly anchored in the WHO Global strategy and plan of action for public health, innovation and intellectual property and positioned within resolution WHA63.28. The difference with this approach is that it aims to:

- Eliminate monopolies on final product, fostered by IP exclusivities
- Implement product development with or without IP protections as long as IP rights are not implemented as the exclusive right to manufacture, sell, or distribute products
- Decentralize systems for manufacturing, distribution and marketing
- Build-in incentives to reward investment in products that have the greatest impact on health outcomes
- Finance a wider range of R&D, including that of neglected diseases
- Foster the development and supply of knowledge as a public good

By embracing new policies that de-link the cost of R&D from product process it is possible to achieve the following:

- Expand access to new innovative products
- Implement targeted R&D incentives
- Establishing a global framework that guides how every aspect of the R&D development value chain will be funded
- The new global norms would replace the current trade agreements that focus on higher prices and stronger product monopolies solely focused on incentives for private for-profit companies.

The main elements of the model, as much as they are still very nuanced and may appear complex, will enable an environment where access and innovation are longer competing objectives requiring trade-offs (Love 2011).

6. Conclusion

Infectious diseases are a global health concern, and more international efforts need be undertaken to research and develop nanomedicines for treatment of infectious diseases; in particular, nanomedicines for the three major killers, i.e. HIV, TB and malaria. Pre-clinical studies demonstrate the potential of nanoparticle drug delivery systems to address some of the drug delivery and treatment challenges of infectious diseases. There are several next generation drug delivery systems and noel therapeutic approaches, which deserve to be explored further (in preclinical and clinical trials) to eventually reach the patient. Innovative commercialization models are in place for development of medicines for infectious diseases. These can be exploited, and possibly refined, to bring more nanomedicines for infectious diseases to the market.

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Tables:

Table 1: List of common infectious diseases, pathogen involved and main transmitting agent.

Disease	Pathogen	Transmitting agent
HIV/AIDS	Human immunodeficiency virus (HIV)	Humans
Tuberculosis (TB)	*Mycobacterium tuberculosis*	Humans
Malaria	*Plasmodium falciparum, Plasmodium vivax*	*Anopheles* mosquito
Dengue fever	Dengue virus 1 - 4	*Aedes* mosquito
Avian Influenza	H5N1, H1N1 etc.	Infected poultry/birds
Zika	Zika virus	*Aedes* mosquito
Sleeping sickness (Human African Trypanosomiasis)	Tsetse fly	*Trypanosoma brucei gambiense*
Ebola	Ebola virus	Humans

Figures

Figure 1: Schematic diagram illustrating the intracellular locality of *M.tb* and HIV pathogens, and the various types of nanoparticles. *M.tb* is typically contained within phagosomes, while HIV virus is located within the nucleus. In most cases nanoparticles will need to penetrate the cellular host/intracellular space and/or nucleus to deliver therapeutic payload.